

## **REMARKS**

### **Allowable Claims**

Claims 12, 13, 14-16 and 19 were found allowable if amended to overcome claim objections and rewritten in independent form. Applicants have amended these claims accordingly thereby placing claims 12, 13, 14-16 and 19 in condition for allowance.

### **Drawings**

Figure 6 was objected to on the basis that the extraneous material was included on the drawing sheet. Applicants have corrected Figure 6 to remove such extraneous information and have provided a substitute sheet of Figure 6 for provisional approval by Examiner Russel.

Further applicants have converted Table 1 to Figure 8 and amended the specification accordingly. An additional drawing sheet has been included showing Figure 8 for provisional approval by Examiner Russel.

### **Statement of Identity**

Applicants filed a Statement of Identity when the present application was originally filed in the USPTO on January 15, 2002. For the convenience of the Office, applicants included herewith a copy of the Statement of Identity that was filed on January 15, 2002. The undersigned attorney attests that the enclosed copy is a true and exact copy of the document filed on January 15, 2002.

### **Rejection of Claims and Traversal Thereof**

In the November 21, 2003 Office Action,

claims 17 and 18 were rejected under 35 U.S.C. §101;

claims 2, 3, 5, 7, 9-11, 13, 17 and 18 were rejected under 35 U.S.C. §112, second paragraph;

claims 1-3, 5-8, 17, 18 and 20 were rejected under 35 U.S.C. §102(b) as being anticipated by WO97/28822 corresponding to U.S. Patent No. 6,500,800 (hereafter referred to as Sobolev '800);

claims 1-3, 5-10, 17, 18 and 20 were rejected under 35 U.S.C. §102(b) as being anticipated by Gopal (U. S. Patent No. 5,670,347);

claims 1-3, 7-11, 17, 18 and 20 were rejected under 35 U.S.C. §102(b) as being anticipated by Gariepy (U. S. Patent No. 5,674,977); and

claims 2-4 were rejected under 35 U.S.C. §103(a) as being obvious over Sobolev '800 and in further view of Blaschuk, et al. (U.S. Patent No. 6,303,576) or Nadler, et al (U. S. Patent No. 5,877,282).

These rejections are hereby traversed and reconsideration of the patentability of the pending claims is therefore requested in light of the following remarks.

**Rejection under 35 U.S.C. §101**

Applicants have amended claims 17 and 18 thereby obviating this rejection. Applicants request that this rejection under 35 U.S.C. §101 be withdrawn.

**Rejection under 35 U.S.C. §112, second paragraph**

Applicants have amended claims 2, 3, 5, 7, 9-11, 13, 17 and 18 according to the suggestions of the Office thereby obviating this rejection. As such, applicants request that this rejection under 35 U.S.C. §112, second paragraph be withdrawn.

**Rejection under 35 U.S.C. §102 (b)**

1. Claims 1-3, 5-8, 17, 18 and 20 were rejected under 35 U.S.C. §102(b) as being anticipated by Sobolev '800. Applicants respectfully traverse this rejection and submit that the claims, as now amended, are not anticipated by the cited reference.

Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, **arranged as in the claim**. *Lindermann Maschinenfabrik GMBH v. American*

*Hoist and Derrick Co.*, 221 U.S.P.Q. 481, 485 (Fed. Cir. 1984) (emphasis added). The cited reference does not meet this standard.

Applicants' amended claim 1 reads as follows:

1. A conjugate for mediating a cell-specific, compartment-specific or membrane-specific transport, wherein the conjugate comprises the following components:

a transport mediator for passing through the cell membrane;  
a cell-specific, compartment-specific or membrane-specific address protein/peptide; and

an active substance to be transported, **wherein the active substance is covalently linked to the address protein/peptide, and wherein a redox cleavage site is present between the transport mediator and the address protein/peptide.**

The Sobolev '800 reference describes a composition that includes and delivers a photosensitive compound into a cell so that destruction of the cell can be effected by radiation. Specifically, the Sobolev '800 structure includes a photosensitive (PS) component; a component that effects target cell recognition and directs transport of the PS compound into the cell; a component that directs transport of the PS component within the cell; and a carrier, **wherein all the components are covalently bonded to the carrier component** as stated at column 5, lines 17 -18 of the Sobolev '800 reference.

The Sobolev '800 reference does not disclose or teach that there is a redox cleavage site present between the transport mediator and the address protein/peptide. Further, as stated above, all the components of the Sobolev '800 structure are covalently bonded to the carrier component and there is no disclosure that describes, teaches or suggest that the components are linked to each other in any fashion. Still further, the Sobolev '800 reference does not in anyway disclose, teach or suggest that the transport mediator is penetratin, transportan or parts thereof, bacterial transport protein or a viral transport protein as recited in applicants' claim 3. Clearly, Sobolev '800 does not disclose each element of applicants' claimed invention and furthermore, the components of the Sobolev '800 structure are not **arranged as in the applicants' claimed invention**. Thus, the Sobolev '800 reference is not anticipatory of the applicants' claimed invention.

Accordingly, applicants respectfully submit that claims 1-3, 5-8, 17, 18 and 20, as amended, are patentably distinguishable over Sobolev '800. Withdrawal of this rejection under 35 U.S.C. §102(b) is requested.

2. Claims 1-3, 5-10, 17, 18 and 20 were rejected under 35 U.S.C. §102(b) as being anticipated by Gopal (U. S. Patent No. 5,670,347, hereinafter Gopal). Applicants respectfully traverse this rejection and submit that the claims, as now amended, are not anticipated by the cited reference.

Gopal describes a synthetic polypeptide that can complex with a DNA molecule. Included in this polypeptide is a DNA-binding sequence that is rich in basic amino acids that binds the DNA molecule. Also included in the synthetic polypeptide is a NLS sequence, which facilitates transport of the DNA into the nucleus. The synthetic polypeptide can be conjugated to a ligand for a target cell receptor. According to the Office this ligand is the equivalent of a transport mediator

Notably, Gopal does not disclose or teach that there is a redox cleavage site present between the transport mediator and the address protein/peptide. Further, Gopal does not in anyway disclose, teach or suggest that the transport mediator is penetratin, transportan or parts thereof, bacterial transport protein or a viral transport protein as recited in applicants' claim 3. Thus, Gopal is not anticipatory of the applicants' claimed invention.

Accordingly, applicants respectfully submit that claims 1-3, 5-10, 17, 18 and 20, as amended, are patentably distinguishable over Gopal. Withdrawal of this rejection under 35 U.S.C. §102(b) is requested.

3. Claims 1-3, 7-11, 17, 18 and 20 were rejected under 35 U.S.C. §102(b) as being anticipated by Gariepy. Applicants respectfully traverse this rejection and submit that the claims, as now amended, are not anticipated by the cited reference.

Gariepy describes a series of peptides (D) that are separated from each other by junctions (J). Importantly all these (D)s and (J)s are assembled on a branched polymeric scaffold to form a octopeptide. This octopeptide can be carried to the nucleus by including the NLS of SV40 t-antigen. According to the Office, a transport mediator is described in Gariepy as multiple CTS domains in the octopeptide. However, Gariepy does not disclose or teach that there is **a redox cleavage site present between the transport mediator and the address protein/peptide**. Further, Gariepy does not in

anyway disclose, teach or suggest that the transport mediator is penetratin, transportan or parts thereof, bacterial transport protein or a viral transport protein as recited in applicants' claim 3. Thus, Garipey is not anticipatory of the applicants' claimed invention.

Accordingly, applicants respectfully submit that claims 1-3, 7-11, 17, 18 and 20, as amended, are patentably distinguishable over Gopal. Withdrawal of this rejection under 35 U.S.C. §102(b) is requested.

#### **Rejection under 35 U.S.C. §103(a)**

Claims 2-4 were rejected under 35 U.S.C. §103(a) as being obvious over Sobolev '800 and in further view of Blaschuk, et al. or Nadler, et al. Applicants submit that the combination of the cited references does not in any way render applicants' claimed invention *prima facie* obvious.

The present invention relates to a conjugate for mediating transport of an active substance into a cell, compartment or through a membrane, wherein the conjugate comprises (1) a transport mediator, for passing through the cell membrane; (2) an address protein and (3) an active substance. Importantly, a redox cleavage site is present between the transport mediator and the address protein/peptide and the active substance is covalently bonded to the address protein/peptide.

As discussed above, Sobolev '800 describes a composition that includes and delivers a photosensitive compound into a cell so that destruction of the cell can be effected by radiation. Specifically, the Sobolev '800 composition includes a photosensitive component (PS); , a component that effects target cell recognition and directs transport of the PS compound into the cell; a component that directs transport of the PS component within the cell; and a carrier, **wherein all the components are covalently bonded to the carrier component** as stated at column 5, lines 17 -18 of the Sobolev '800 specification. Notably, Sobolev '800 does not in anyway disclose, teach or suggest that a redox cleavage site is present between the transport mediator and the address protein/peptide and does not disclose that the transport mediator is selected from the group consisting of: a penetratin, a penetratin derivative, transportan or parts thereof, bacterial transport protein and viral transport protein

In attempt to overcome the shortcomings of Sobolev '800, the Office proposed a combination of Sobolev '800 with Blaschuk, et al. or Nadler, et al because according to the Office, both references describe the penetratin as a transport mediator.

Initially, it should be noted that in order to determine obviousness, it is incumbent upon the Office to view the invention as a whole. *In re Wesslau*, 174 U.S.P.Q. 393 (CCPA 1965). Also, the Office must **consider the inventions of the cited references in their entireties**. Certain individual features from the references may not be chosen and merely lumped together as a mosaic in an attempt to meet the features of the rejected claims. This legal concept is important for the Office to remember when attempting to combine prior art that teach entirely different structures.

The polypeptide inhibitors of Nadler, et al. include a signal sequence and at least two NSLs. Importantly, the NSLs are covalently linked to the signal sequence polypeptide. Clearly, the Nadler, et al. structure is entirely different from that of Sobolev '800 and applicants question the combinability of such references. Applicants assert that if the teachings and structures of Sobolev '800 and Nadler, et al. are combined then each individual structures will be rendered unsatisfactory for its intended use or change the principle of operation, and thus the combination does not establish a *prima facie* case of obviousness. *See, In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

If the signal sequence of Nadler, et al., that must be covalently bonded to the NSLs in the Nadler, et al. structure, is incorporated into the Sobolev '800 structure, applicants question placement of such signal sequence and whether it is covalently bonded to the carrier support framework of Sobolev '800 or still covalently bonded to the NSL. There is no teaching or guidance in either reference for this specific transfer of elements and/or instructions for inclusion of the signal sequence into the Sobolev '800 structure. Keeping in mind that the Office is not allowed to pick and choose certain elements of Nadler, et al. to the exclusion of other elements, applicants submit that the Office cannot pick just the signal sequence of Nadler, et al. and disconnect it from the NSLs for inclusion into the Sobolev '800 structure without some suggestion to proceed in that direction.

Furthermore, the Sobolev '800 reference teaches that all components are covalently bonded to the carrier material and inclusion of the Sobolev '800 components into the Nadler, et al. structure, including the binding to a carrier component would change the entire function and structure of Nadler, et al. Clearly, the references provide no teaching or suggestion for attempting to recreate applicants' claimed invention.

Applicant points out that obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination and

suggesting the desirability of the combination. Applicant respectfully submits that the Office's statement that "the claimed invention would be obvious to one having ordinary skill in the art" is not sufficient by itself to establish *prima facie* obviousness. According to the Board in *Ex parte Obukowicz*, 27 U.S.P.Q. 2d 1063, 1065 (B.P.A.I. 1992):

"In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art....The examiner can satisfy this burden only by showing some **objective** (emphasis added) teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teaching of the references."

See also *Ex parte Humphreys*, 24 U.S.P.Q. 2D 1255, 1262 (B.P.A.I. 1992) where the Board addressed this very issue and determined the Office was wrong in rejecting the claims for obviousness because the examiner's rejection was not **specific** as to how one of ordinary skill in the art would have found it obvious to combine the references. Furthermore, the Board noted the examiner had not explained with any **specificity what areas of the references would suggest the combination**. This is the circumstance here. The Office has not identified any objective or specific motivation or suggestion in the cited references that would motivate one skilled in the art to combine the references. Thus, the Office seems to be merely reinterpreting the prior art in light of applicant's disclosure, in order to reconstruct applicant's claimed invention, but without any instructional or motivating basis in the references themselves. Such approach is improper and legally insufficient to establish any *prima facie* case of obviousness.

The Office proposes that the two references can be combined to teach and suggest applicant's claimed invention. However, even if the two references were attempted to be combined (despite the absence of any proper basis for such combination), the resultant combination would still not embody every limitation required by applicant's claimed invention. Specifically, the combination would still **not** describe, teach or suggest **a redox cleavage site between the transport mediator and the address protein/peptide**. Further, applicants submit that the Office failed to give weight to the advantages and benefits of the present invention as part of the "invention as a whole" and cited references that do not disclose or teach a redox cleavage site between the transport mediator and the address protein/peptide. Importantly, this redox cleavage site insures that the transport mediator is cleavable from the address protein/peptide and providing for a more effective transport of the active substance to the final destination. Further, the conjugate is stable in the extracellular environment, but is cleaved in the cytosol by naturally occurring enzymes that prevent the undesired transfer of the transport peptide to

the target component. Obviously, neither the combination of cited references nor the individual references recognize the benefits of the present invention.

In conclusion, the proposed combination does not render applicants' claimed invention *prima facie* obvious because there is no motivation, suggestion or basis in Sobolev '800 and Nadler, et al. to combine the two references; both structures would no longer function as intended if combined, and all the recited features of applicants' claimed invention are not in any way disclosed or suggested in the cited references. Accordingly, applicants respectfully request withdrawal of the rejection of claims 2-4 under 35 U.S.C. §103(a) based on Sobolev '800 in view of Nadler, et al.

The Office has also cited Blaschuk, et al. in combination with Sobolev '800 as a combination that defeats the patentability of claims 2-4. Applicants submit that this proposed combination does not render applicants' claimed invention *prima facie* obvious.

Blaschuk, et al. describes methods and compounds that inhibit  $\beta$ -catenin mediated gene transcription and cellular differentiation. The structures of Blaschuk, et al. include a modulating agent and optionally an **internalization sequence covalently linked to the modulating agent** (see column 1, lines 60-64 of the Blaschuk, et al. specification). Blaschuk, et al. further states that this internalization sequence can include the amino acid sequence "RQIKIWFQNRRMKWKK."

Applicants assert that the combination of Blaschuk, et al. and Sobolev '800 suffers from the same deficiencies as that of Nadler, et al and Sobolev '800. Specifically, the structure of the Blaschuk, et al. is entirely different from that of Sobolev '800. As in the Nadler, et al. structure, the structure of Blaschuk, et al. must include a covalent bond between the modulating agent and the internalization sequence while the structure of Sobolev '800 includes bonding all components directly to the carrier backbone. There is no teaching or guidance in either reference for the transfer and placement of the internalization sequence of Blaschuk, et al. for inclusion into the Sobolev '800 structure. Further, the Office has not identified any objective or specific motivation or suggestion in the cited references that would motivate one skilled in the art to combine the references.

Still further, the proposed combination does not teach or suggest all applicants' claimed elements. Specifically, this combination, like the last combination does not teach or suggest a redox cleavage site between the transport mediator and the address protein/peptide, nor does it recognize the benefits of such a cleavable bond.



In conclusion, the proposed combination does not render applicants' claimed invention prima facie obvious because there is no motivation, suggestion or basis in Sobolev '800 and Blaschuk, et al. to combine the two references; both structures would no longer function as intended if combined, and all the recited features of applicants' claimed invention are not in any way disclosed or suggested in the cited references. Accordingly, applicants respectfully request withdrawal of the rejection of claims 2-4 under 35 U.S.C. §103(a) based on Sobolev '800 in view of Blaschuk, et al.


**Petition for Extension of Time/Fees Payable**

Applicants hereby petitions for a one (1) month extension of time, extending the deadline for responding to the November 21, 2003 Office Action from February 21, 2004 to March 21, 2004. The entry of this petition results in a petition fee of \$55.00. Applicants have added two new independent claims, with a fee increase of \$86.00. A credit card payment form in the amount of \$141.00 is submitted herewith in payment of the petition fee and additional claims. The U.S. Patent and Trademark Office is hereby authorized to charge any additional amount necessary to the entry of this amendment, and to credit any excess payment, to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

**Conclusion**

Applicants have satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Russel reconsider the patentability of claims 1-11, 13, 17, 18 and 20 in light of the distinguishing remarks herein, and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Russel is requested to contact the undersigned attorney at (919) 419-9350 to resolve same.

Respectfully submitted,

  
Marianne Fuierer  
Registration No. 39,983  
Attorney for Applicants

Telephone: (919) 419-9350  
Facsimile: (919) 419-9354  
IPTL File: 4121-133